REMARKS/ARGUMENTS

Amendments to the Specification

Paragraph 29 was amended to set forth a sequence of expressed CAIX of SEQ ID NO:1. Support for this recital is found in the specification in the last sentence of paragraph 29 which incorporated by reference the sequence subject matter of U.S. Patent No. 6,297,051. The CAIX coding sequence of SEQ ID NO:1, and protein sequence of SEQ ID NO:2 are those reported in the '051 patent in SEQ ID NOS: 1 and 2 thereof, respectively.

Accordingly, the Applicants believe the amendments to the specification add no new matter and respectfully request their entry.

The Sequence Listing

In accordance with the above amendment to the specification, the Applicants request entry of the enclosed sequence listing into the specification in adherence with 37 C.F.R. §§1.821 to 1.825. This amendment contains SEQ ID NOS:1 and 2 in computer readable form (CRF) and a paper copy of the sequence information which has been printed from the computer readable form. The information contained in the computer readable form was in part prepared through the use of the software program "FastSEQ 4.0" and is identical to that of the paper copy.

Applicants have amended the specification in order to correctly identify the SEQ ID NOS. Support for this amendment is found as described immediately above. Accordingly, these amendments add no new matter.

Status of the claims

Claims 1-25 are pending with claims 4, 24 and 25 standing withdrawn. Claims 1-3 and 5-23 to the extent the CAIX is a polypeptide have been examined on the merits. Claims 1, and 14 are presently amended. Claims 2, 3, 6, 24 and 25 are presently canceled without prejudice. Claim 26 is newly presented. After entry of these amendments, claims 1, and 4, 5, 7 to 23 and 26 will be pending with claim 4 standing withdrawn.

Claims 1-3 and 5-23 are rejected under 35 U.S.C. 112, first paragraph, as failing

to comply with the written description requirement.

Claims 1-3, 6-14 and 16-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 6-1 4 and 16-23 stand rejected under 35 U.S.C. 102(b) as being allegedly anticipated by Zisman et al. (Journal of Clinical Oncology 19(6): 1649-1 657, March 15, 2001)

Claims 3, 5-1 1, 14-16 and 18-23 stand rejected under 35 U.S.C. 102(b) as being allegedly anticipated by U.S. Patent number 5,955,075 (issued September 21, 1999).

Applicants respond to these rejections below.

The Restriction Requirement

Applicants wish to correct the record. The Action alleges that the Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement and thus failed to timely traverse the Restriction Requirement. At length, the Applicants detailed the factual and legal arguments which distinctly and specifically addressed the concerns identified by the Examiner. In that response, for instance, the Applicants set forth why the Ivanov reference, which was alleged to anticipate the claims, did not in fact anticipate them and thus did not negate the Unity of Invention of this national stage application.

Amendments to the claims.

Claim 1 was amended to set forth immunohistochemical staining or immunoassays. Support for this subject matter is found *interalia* at paragraphs 38 and 39. Claim 1 was further amended to set forth clear cell carcinoma. Support for this subject matter is found inter alia in original claim 2 and paragraph 58, first sentence. Support for the subject matter of SEQ ID NO:2 is as discussed with respect to the amendments to the specification. Support for the subject matter of the quantification percentage is found in the specification at p. 34. Support for association between the higher quantification percentage and the prognosis is found in the specification at p. 13 and paragraph 78. Support for the recital of *human* is found in paragraph

37 and more particularly at Ex. 1, p. 58. Support for the recital of "about" can be found *inter alia* in paragraphs 66 and 74.

Support for amendments to claim 14 are as set forth above for claim 1.

New claim 26 finds support as set forth above with respect to the amendments to the specification.

Accordingly, the Applicants believe the amendments to the claims add no new matter and respectfully request their entry.

Response to the rejection of claims 1-3, 6-14 and 16-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention.

The Action was concerned with the potential breadth of the CAIX subject matter of the claims. To the extent that the concerns addressed CAIX nucleic acid subject matter, the Applicants note that the claim 1 has been amended to set forth CAIX protein subject matter and that claim 14 already recited CAIX polypeptide. Without acquiescing on the merits and in the spirit of expediting prosecution, the applicants have further amended the base claims to set forth a human CAIX protein. In addition, new claim 14 sets forth that the immunohistochemistry methods or immunoassays use antibodies reactive with a protein of SEQ ID NO:2 to quantify the expressed CAIX protein.

With these amendments, the Applicants believe they have done more than the law requires. There is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure (see, Falkner vs. Inglis, 448 F.3d 1357, 1363 (Fed. Cir. 2006). Indeed, the Court in Falkner held that

> "where, as in this case, accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences (here "essential genes"), satisfaction of the written description requirement does not require either the recitation or incorporation by reference[14] (where permitted) of such genes and sequences."
>
> [14] Here, the patentee did not attempt incorporation by reference. Where, of course, certain material that is not present in the specification is deemed nonessential to the satisfaction of the written description requirement, the issue of proper incorporation by reference *vel non* is irrelevant.

In view of such precedent, it is more than enough that the Applicants point at length to the literature (see, paragraph 29 of the specification), setting forth the pertinent subject matter, and incorporate by reference such subject matter by virtue of paragraph 78 of the specification. This literature amply addresses the subject matter of CAIX protein and its detection in humans. With respect to the detection of a fragment of an expressed protein as opposed to the whole of the expressed protein, detection of the fragment speaks to the expression of the whole. Moreover, regardless of any supposed human variation in CAIX protein sequences, the Applicants applied their method to expressed CAIX in a cohort of ***321*** patients (*see*, the Example at p. 20) and amply demonstrated in Example 1 that they were in possession of the claimed subject matter with respect to a large human population. These results speak to the general applicability of their claimed methods.

Accordingly, as a person of ordinary skill in the art would readily appreciate that the Applicants were in possession of the claimed invention at the time of filing, the Applicants respectfully request that this grounds of rejection be reconsidered and withdrawn.

Response to the rejection of claims 1-3, 6-14 and 16-23 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Action was concerned that it was not clear how the quantification was implemented. Without acquiescing on the merits and in the spirit of expediting prosecution, the applicants have amended the base claims to set forth immunohistochemical staining or immunoassay techniques. Accordingly, the Applicants respectfully request that this grounds of rejection be reconsidered and withdrawn.

Response to the rejection of claims 1-3, 6-1 4 and 16-23 under 35 U.S.C. 102(b) as being allegedly anticipated by Zisman et al. (Journal of Clinical Oncology 19(6): 1649-1 657, March 15, 2001) (hereinafter, Zisman)

To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

A. Standard for anticipation

For a rejection of claims under § 102 to be properly founded, the Examiner must establish that a single prior art reference either expressly or inherently discloses each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Verdegaal Bros. V. Union Oil Co. Of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

In *Scripps Clinic & Research Found. v. Genentech, Inc.*, 18 USPQ2d 1001 (Fed. Cir. 1991), the Federal Circuit held that:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . . There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Id.* at 1010.

Anticipation can be found, therefore, only when a cited reference discloses all of the elements, features, or limitations of the presently claimed invention.

Here, the proffered rejection fails meet this test. Claim 1 recites:

> A method of aiding in a renal cell carcinoma prognosis, the method comprising:
>
> (a) quantifying, by immunohistochemical staining or immunoassay, expressed carbonic anhydrase IX (CAIX) of SEQ ID NO:1, if any, present in one or more samples derived from a renal tumor and/or a metastatic lesion derived from a renal tumor of a human subject diagnosed with renal clear cell carcinoma to produce quantified CAIX expression data indicating the overall quantification percentage of the sample(s) positive for CAIX expression;
>
> (b) correlating the quantified CAIX expression data with a probability of a renal cell carcinoma prognosis for the subject, wherein subjects having a lower quantification percentage than about 85% are predicted to have a worse outcome for those subjects with locally advanced renal clear cell cancer and poor survival for those subjects with metastatic renal clear cell cancer.

The cited passage in Zisman fails to mention or even suggest carbonic anhydrase IX (CAIX) as set forth in the above claim or as set forth in independent claim 14. Instead, the passage merely recites:

> Finally, the relationship between the newly formed integrated staging system and the possible prognostic variables was examined using a forward stepwise procedure of the Cox

> proportional hazards model after including the UISS staging system as the first entry. We also analyzed the distribution of different histological groups in order to examine whether the UISS picks up differences in survival imposed by histologic variation. We used a stepwise modeling algorithm with a 0.10 significance level for entering and 0.15 for removing explanatory variable. Data obtained were analyzed using Stata statistical software, 6.0 release (Stata Corp, College Station, TX).

The histologic variation disclosed in Zisman is not CAIX, but sarcomatoid vs. all others in Table 4 and its footnote, or Table 5 at p. 1655 of Zisman. In Table 6 on p. 1656 of Zisman, the histological types are papillary, clear cell & chromophobe type, and sarcomatoid & collecting duct.

As Zisman does not disclose the CAIX subject matter of either base claim, it simply can not negate the novelty of the pending claims. Accordingly, the Applicants respectfully request that this grounds for rejection be reconsidered and withdrawn.

Response to the rejection of claims 1-3, 5-11, 14-16 and 18-23 under 35 U.S.C. 102(b) for alleged anticipation by U.S. Patent number 5,955,075 (issued September 21, 1999) (hereinafter, Zavada).

Each of the base claims, as amended, now sets forth that a lower quantification percentage is associated with a poorer outcome for subjects with clear cell carcinoma. Zavada, in contrast, does not disclose or suggest this relationship. Zavada states at col. 58, lines 39:

> The results recorded in this example indicate that the presence of MN proteins in a tissue sample from a patient may, in general, depending upon the tissue involved, be a marker signaling that a pre-neoplastic or neoplastic process is occurring. Thus, one may conclude from these results that diagnostic/prognostic methods that detect MN antigen may be particularly useful for screening patient samples for a number of cancers which can thereby be detected at a pre-neoplastic stage or at an early stage prior to obvious morphologic changes associated with dysplasia and/or malignancy being evident or being evident on a widespread basis.

In short, Zavada teaches that CAIX/MN signals a pre-neoplastic or neoplastic process. Accordingly, it teaches away from the present invention which found surprisingly a *lower* quantification percentage for CAIX (which would correspond to a lesser amount of Zavada's pre-

neoplastic or neoplastic process) actually indicated a with *worse* prognosis for patients *already* diagnosed with locally advanced or metastatic clear cell renal cancer.

Ivanov et al., previously cited by the Examiner, similarly taught:

> We conclude that the cell surface *trans*-membrane carbonic anhydrases CA IX and CA XII are overexpressed in many tumors suggesting that this is a common feature of cancer cells that may be required for tumor progression. These enzymes may contribute to the tumor microenvironment by maintaining extracellular acidic pH and helping cancer cells grow and metastasize. Our studies show an important causal link between hypoxia, extracellular acidification, and induction or enhanced expression of these enzymes in human tumors.

Accordingly, the Applicants' findings are not disclosed or suggested by the cited art which expected that higher levels of CAIX expression would favor worse outcomes.

As nothing in Zavada suggests a method based upon the counter-intuitive relationship identified by the Applicants and now expressly set forth in the base claims, the Applicants respectfully request that this grounds of rejection be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

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Attachments
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